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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/371,347	08/10/1999	ROY A. GRAVEL	50004/003003	9130

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EXAMINER	
RAMIREZ, DELIA M	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 05/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/371,347	GRAVEL ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,36-38,41-43,45-49 and 52-55* is/are pending in the application.

4a) Of the above claim(s) *48 and 49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,36,37,41-43,45-47 and 52-55* is/are rejected.

7)☒ Claim(s) *3 and 38* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 1-5, 36-38, 41-43, 45-49, 52-55 are pending.

Applicant's amendment of claims 1-5, 36-38, 41-43, 45-47, 52-53, and addition of claims 54-55 in a communication filed 3/4/2004 is acknowledged.

Claim 47, as amended, now recites the elected species, i.e. SEQ ID NO: 25 as well as non-elected species. Claim 47 will be examined to the extent it encompasses the elected species.

Claims 48-49 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Drawings

1. The drawings submitted on 3/4/2004 are approved by the Examiner.

Claim Rejections - 35 USC § 112, Second Paragraph

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 5, 41-43, 45-46, 52-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claims 5, 41-43, 53 and 55 (claims 52-53 dependent thereon) are indefinite in the recitation of "complementary" or "complement" because it is unclear which "complements" are encompassed by the claims. Fragments of any size which are complementary to the polynucleotides claimed can be considered as "complements". Applicants have not define the term "complement", as it relates to size, in

the specification either. If applicants wish to claim the entire complementary sequence, it is suggested that the term "complementary" be replaced with "completely complementary" and the term "complement" be replaced with "complete complement". Correction is required.

5. Claims 45-46 are indefinite in the recitation of "polypeptide having X% of the biological activity of the methionine synthase reductase polypeptide of SEQ ID NO: 2" as it is unclear which "biological activity" is being referred to. The term "biological activity" can have many different interpretations to one of skill in the art. For example, one interpretation of the term "biological activity" in regard to polypeptides is the ability to elicit antibodies. It is suggested that the term "biological activity" be replaced with a term that clearly defines Applicant's intended biological function. For examination purposes, it will be assumed that the term reads "polypeptide having X% of the methionine synthase reductase activity of the polypeptide of SEQ ID NO: 2". Correction is required.

6. Claims 53 and 55 are indefinite in the recitation of "the complement of which comprises a naturally-occurring mammalian methionine synthase reductase mutation or polymorphism" or "the complement of said polynucleotide sequence comprises a naturally-occurring mammalian methionine synthase reductase mutation or polymorphism" for the following reasons. The specification discloses that a mutation or a polymorphism can be single nucleotide substitution or a deletion of a limited number of nucleotides. Therefore, in the absence of a structural limitation defining the area comprising the naturally-occurring mutation/polymorphism, and in the absence of a limitation defining which specific mutations/polymorphisms are encompassed by the claims, it is unclear as to how the term further limits the claims.

Applicants submit that this rejection should not be applied to amended claim 53 or new claim 55 since as recited it indicates that the mutation or polymorphism in the mammalian methionine synthase reductase gene is one that is naturally found in the MTRR gene and is not artificially generated. Applicant's arguments are not found persuasive. While it is agreed that the term refers to a naturally-

occurring mutations/polymorphism found in the MTRR gene, it is noted that neither claim 53 or 55 recite a limitation indicating that the nucleic acid is indeed a mammalian methionine synthase gene. Since the nucleic acids of these claims can be of any function, the rejection is applied for the reasons indicated above. It is noted that the rejection was not applied to claim 54 since that nucleic acid has to encode a mammalian methionine synthase reductase. For examination purposes, it will be assumed that the term reads "the complete complement of which comprises a fragment of any mammalian methionine synthase reductase nucleic acid, wherein said fragment comprises a naturally-occurring mammalian synthase reductase mutation or polymorphism". Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-2, 4-5, 36-37, 41-43, 45-47, 52-53 remain rejected and new claims 54-55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polynucleotides of SEQ ID NO: 1, 41, 43, 45, and 47, does not reasonably provide enablement for (1) polynucleotides encoding a mammalian methionine synthase reductase having at least 90%, 50%, or 85% sequence identity to SEQ ID NO: 1, 41, 43, 45 and/or 47, (2) polynucleotides which are at least 50%, 85%, or 95% sequence identical to SEQ ID NO: 1, 41, 43, 45 or 47, and are capable of reducing expression of an mRNA encoding a methionine synthase reductase, (3) polynucleotides which hybridize at specific conditions to the polynucleotides of SEQ ID NO: 1, 41, 43, 45 or 47, and are capable of reducing expression of an mRNA encoding a methionine synthase reductase, (4) polynucleotides encoding a mammalian methionine synthase reductase having at least 90% or 50% sequence identity to SEQ ID NO: 1, 41, 43, 45, or 47, wherein the methionine synthase reductase has at least 20-30% or 55-

75% of the biological activity of the polypeptide of SEQ ID NO: 2, (5) polynucleotides encoding a mammalian methionine synthase reductase further comprising a consensus binding site for FAD, FMN, or NADPH, wherein the polynucleotides have at least 90% or 50% sequence identity to SEQ ID NO: 1, 41, 43, 45 or 47, or (6) the complete complements of the polynucleotides of (2) or (3) which comprises a fragment of any mammalian methionine synthase reductase nucleic acid, wherein said fragment comprises a naturally-occurring mammalian synthase reductase mutation or polymorphism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection has been discussed at length in Paper No. 28, mailed on 8/12/2003.

9. Applicants argue that the claims have been amended to add a structural limitation and a functional limitation. Applicants also submit that practicing the full scope of the claims would not require undue experimentation since the specification teaches (1) primers for amplifying and sequencing a methionine synthase reductase nucleic acid such that one could determine the level of sequence identity, (2) high stringency conditions to identify nucleic acids which would hybridize to the polynucleotides of SEQ ID NO: 1, 41, 43, 45 and 47, (3) assays to determine methionine synthase reductase activity and how to quantify this activity, and (4) how to determine if a nucleic acid is able to modulate the level of expression of a polynucleotide encoding a methionine synthase reductase, such as ELISA and PCR.

10. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the instant rejection as it relates to claims 1-2, 4-5, 36-37, 41-43, 45-47, 52-53 or to avoid the rejection of new claims 54-55. Claims 1-2, 36-37, 45-47 and 54 are directed to (1) polynucleotides encoding polypeptides having methionine synthase reductase activity wherein said polynucleotides have 90%, 85% or 50% to the polynucleotides of SEQ ID NO: 1, 41, 43, 45, or 47, (2) the polynucleotides of (1) wherein the polypeptides they encode have a specific percentage of the methionine synthase reductase activity of the polypeptide of SEQ ID NO: 2, (2) the polynucleotides of (1) further comprising a naturally-occurring

mammalian methionine synthase reductase mutation or polymorphism. Claims 4-5, 41-43, 52-53 and 55 are directed to polynucleotides encoding polypeptides which can decrease the expression of a methionine synthase reductase polynucleotide and (1) hybridize under specific conditions to the polynucleotides of SEQ ID NO: 1, 41, 43, 45 or 47, or (2) have a specific sequence identity to the polynucleotides of SEQ ID NO: 1, 41, 43, 45 or 47. While it is agreed that (1) the specification teaches primers, and an assay to determine methionine synthase reductase activity, and (2) one of skill in the art would know how to calculate % sequence identity, how to quantify enzymatic activity, ELISA and PCR, the Examiner disagrees with Applicant's contention that this knowledge is sufficient to enable the full scope of the claims. The specification is completely silent regarding which are the structural elements in the polynucleotides of SEQ ID NO: 1, 41, 43, 45 and 47 which can be modified to create 90%, 85% or 50% sequence identical homologs which encode methionine synthase reductases. Furthermore, the specification is silent in regard to which are the structural elements which can be modified in the polynucleotides of SEQ ID NO: 1, 41, 43, 45 and 47 such that the structural homologs recited in the claims encode polypeptides having 20-30% or 55-75% of the methionine synthase reductase activity of the polypeptide of SEQ ID NO: 2. It is reiterated herein that the state of the art already discussed in the previous Office Action teaches the unpredictability of accurate determination of functions solely on structural homology. Therefore, in the absence of additional information correlating function with the structures disclosed, providing the structure and function of the polynucleotides of SEQ ID NO: 1, 41, 43, 45 and 47 is not deemed sufficient to allow one of skill in the art to practice the full scope of the claimed invention without undue experimentation. While the specification discloses two polymorphisms and two mutations in the polynucleotide of SEQ ID NO: 1, the specification is completely silent in regard to other naturally-occurring polymorphisms or mutations in the structural homologs recited in the claims. The specification fails to provide any clue as to other biological functions for the polynucleotides of

claims 4-5, 41-43, 52-53 and 55. Thus, determining these functions would also require undue experimentation.

Allowable Subject Matter

11. Claims 3 and 38 appear to be allowable over the prior art of record but are objected to since they depend upon rejected base claims.

Conclusion

12. No claim is in condition for allowance.

13. Applicant's amendment of claims 1-5, 36-38, 41-43, 45-47, 52-53 and addition of claims 54-55 necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 872-9306. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be

retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

15. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
May 12, 2004

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600